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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,116	11/20/2001	John H. Healey	9958-004-999	6037

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n N .	Applicant(s)	
	09/890,116	HEALEY ET AL.0	
	Examin r	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The amendment filed 27 September 2004 has been received and entered. Claim 70 has been amended and new claims 77-121 have been added. Claims 38-121 are pending to which the following grounds of rejection are or remain applicable.

Response to Arguments

1. The rejection made in the paper mailed 24 June 2004 under 35 U.S.C. §103(a) over Anuta and Lehtinen is maintained and hereby repeated for the reasons set forth in the previous office action and those set forth below.

Applicant argues that Lehtinen et al do not apply to the repair of bony deficits in flat bones, i.e. spine following tumor removal to inhibit tumor recurrence and enhance the support capacity of the remaining bone. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., repair of bony deficits in flat bones) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Further, applicant asserts that the instant invention is drawn to the particular particle size distribution of the anti-resorptive agent, whereby, a uniform mixture will prevent clumping and promote an even distribution of the anti-resorptive agent and prevent the agent from seeping out at different rates and/or in different peripheral areas. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the

method of promoting even distribution of the anti-resorptive agent) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

It would have been made obvious to one of ordinary skill in art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It does not teach the addition of bisphosphonates. It would have been obvious to employ a bisphosphonate in the bone cement motivated by the teaching of Lehtinen who teaches that bisphosphonate's main effect is their ability to inhibit bone resorption (column 3, lines 21-23). Such a modification would have been motivated by the reasoned expectation of producing a bone-cement, which is effective in comprehensively inhibiting bone resorption.

2. The rejection made in the paper mailed 24 June 2004 under 35 U.S.C. §103(a) over Mao and Gayer is maintained and hereby repeated for the reasons set forth in the previous office action and those set forth below.

Applicant maintains that the claimed invention seeks to arrest the process of aseptic loosening attributed to osteoclasts and associated with cemented prosthesis. In response to applicant's argument that the references fail to show certain features of

applicant's invention, it is noted that the features upon which applicant relies (i.e., the method of arresting the process of aseptic loosening attributed to osteoclasts) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 116 recites the limitation "the composition of claim 1" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim because claim 1 has been cancelled.

Claim 118 recites the limitation "an effective amount of the composition of claim 1" in lines 4-5 of the claim. There is insufficient antecedent basis for this limitation in the claim because claim 1 has been cancelled.

The examiner realizes that this deficiency was discussed in the interview dated 21 October 2004, however, the applicant must correct this deficiency. See MPEP §1302.04 [R-2]

Election/Restrictions

Newly submitted claims 118-121 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the methods presented for inhibiting growth of or killing residual cells adjacent to the bone cement comprising contacting a spine, limb or bone which has undergone tumor resection with an effective amount of claim 1 (38, 54, 77 and 93) was not presented. Only composition claims were originally presented.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 118-121 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 54, 61, 70, 77, 78, 80, 86, 93, 98, 100 and 109 are rejected under 35 U.S.C. 102(a) as being anticipated by Sabokbar et al. (Ann. Rheum. Dis. October 1998).

Sabokbar et al. teach a polymethylmethacrylate (PMMA) bone cement, mixed with the bisphosphonate, etidronate, to inhibit bone resorption (see abstract). Specifically, PMMA was mixed with crushed etidronate and then polymerized according to manufacturer's instructions (see Methods). The extent of resorption was significantly less in the PMMA with etidronate than in PMMA alone suggesting that incorporation of a bisphosphonate into bone cement to inhibit macrophage-osteoclast differentiation may effectively be used to control periprosthetic osteolysis (see discussion). Sabokbar et al. teach that bisphosphonates, included in bone cement may be used to prevent or to control the bone resorption seen in aseptic loosening (see discussion).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 38-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anuta U.S. Patent No. 4,341,691 and Sabokbar et al.

The claims are drawn to a composition comprising a polymeric bone cement in the form of particles and an anti-resorptive agent in the form of particles wherein the anti-resorptive agent's particle-size distribution is about the same or less than that of the

polymeric bone-cement component's particle size distribution with dependent claims drawn to bisphosphonates, cholesterol lowering agents, estrogen-bisphosphonate conjugates and gallium as anti-resorptive agents and particle size's of 75 to 70 % with an average diameter of about 25 microns and about 30 to 35 % with an average diameter of about 13 to 17 microns.

Anuta teaches that the polymethylmethacrylate (PMMA) powder in Zimmers standard bone cement is comprised of a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It does not teach the addition of a bisphosphonate.

Sabokbar et al. teach PMMA cement with the bisphosphonate etidronate incorporated into the bone cement. The composition is mixed and polymerized. When crushed, the PMMA/Etidronate has a particle size of between 1 and 10 microns. Sabokbar et al. teach that the addition of bisphosphonates with PMMA bone cement can inhibit PMMA induced osteoclast generation and bone resorption and inhibit wear debris induced osteolysis and provide a therapeutic approach to prevent aseptic loosening.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5,

lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63) and add the bisphosphonate powder of Sabokbar, such a modification would have been motivated by the reasoned expectation of producing a bone cement composition which is effective in comprehensively preventing osteoclast formation and loosening of prostheses. Additionally, It is prima facie obvious to substitute equivalents, i.e. etidronate for other bisphosphonates not recited, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532.

Claims 54-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabokbar et al and Claims 54-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabokbar et al. and Anuta as applied to claims 38-53 above, and further in view of Merck and Co, Inc. WO 96/39107.

The claims are drawn to a composition comprising a bone-cement and an anti-resorptive agent in a sufficient amount that does not compromise the cement's chemical or mechanical properties but sufficient to prevent loosening of the bone cement from living bone, dependent claims are drawn to the amount of anti-resorptive agent added to the bone cement, and an amount of anti-resorptive agent that is not toxic to osteoblast while toxic to osteoclasts. Further dependent claims are drawn to the particle size

wherein 65 to 70 percent of the particles have an average diameter of about 25 diameters and 30-35 percent of the particles are about 13 to 17 microns in diameter.

Anuta teaches that the polymethylmethacrylate (PMMA) powder in Zimmers standard bone cement is comprised of a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It does not teach the addition of a bisphosphonate.

Sabokbar et al. teach PMMA cement with the bisphosphonate etidronate incorporated into the bone cement. The composition is mixed and polymerized. When crushed, the PMMA/Etidronate has a particle size of between 1 and 10 microns. Sabokbar et al. teach that the addition of bisphosphonates with PMMA bone cement can inhibit PMMA induced osteoclast generation and bone resorption and inhibit wear debris induced osteolysis and provide a therapeutic approach to prevent aseptic loosening.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63) and add the bisphosphonate powder of Sabokbar, such a modification would have been motivated by the reasoned

expectation of producing a bone cement composition which is effective in comprehensively preventing osteoclast formation and loosening of prostheses. It does not teach the addition of other bisphosphonates.

Merck and Co. teach the addition of further bisphosphonates to the cement. The bisphosphonate applicable in the cement includes the free acids and pharmaceutically acceptable salts and barium salts of alendronate, clodronate, tiludronate, YM 175, ibandronate, risedronate, piridronate, pamidronate or combinations thereof (see page 5). Inhibition of bone resorption is used to refer to bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity (see page 6). The term "cement" encompasses the mixed cement composition containing all the ingredients and components prior to, during and after complete curing (see page 7). The PMMA beads have a substantially uniform particle size of about 5 to 20 microns average diameter (page 7 last paragraph). The polymer powder part can also contain a radiopaquing agent e.g. barium sulfate (page 8, 2nd paragraph). The amount of bisphosphonate is generally from 0.005 to 10 percent of the total cement composition. It would have been made obvious to one of ordinary skill in art at the time it was made to add additional bisphosphonates as cited in Merck and Co. Such a modification would have been motivated by the reasoned expectation of producing a bone cement/bisphosphonate composition which is effective in comprehensively preventing formation of osteoclasts and loosening of prosthetic implants.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/6/05

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